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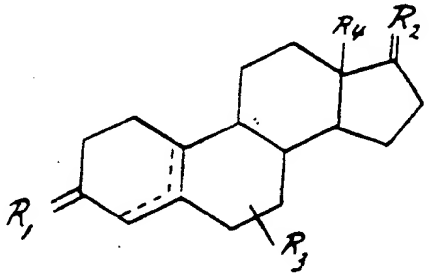
(54) Title: PHARMACEUTICAL PREPARATION CONTAINING A FLUORIDE SALT



(I)

(57) Abstract

The invention relates to a pharmaceutical preparation containing a fluoride salt and a steroid with the general formula (I), wherein R_1 = H_2, H(OR_5) or O; R_2 = (αR_6) (βOR_7; R_3 = H or (1-4 C)alkyl in position 6 or 7; R_4 = (1-4 C)alkyl; R_5 = H or (1-18 C)acyl; R_6 = H or (1-4 C)hydrocarbon radical; R_7 = H or (1-18 C)acyl; and the broken lines indicate the presence of an additional bond in the 4,5- or 5,10-position.

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Pharmaceutical preparation containing a fluoride salt.

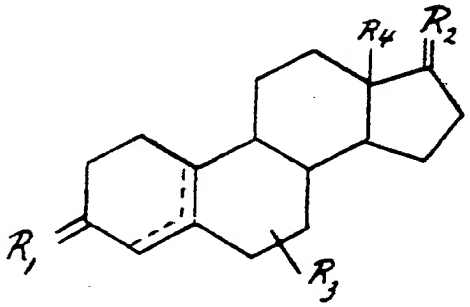
The invention relates to a pharmaceutical preparation containing a fluoride salt.

Such preparations are known, in particular for treating osteoporosis. Fluoride salts such as, for example, NaF and Na_2PO_3F stimulate the trabecular bone substance and are therefore suitable for treating osteoporosis. A disadvantage of such preparations is that they cause cortical bone loss and a change in the structure of the cortical bone. As a consequence thereof, the bone becomes more brittle, which has in turn the consequence that more frequent and ready bone fractures, in particular hip fractures, occur.

It is further known that bone-protecting steroids are used to prevent and/or treat osteoporosis and more generally, diseases which are the result of excessively low bone substance.

Surprisingly, it has now been found that by using certain steroids in combination with said fluoride salts for preventing and/or treating such diseases and, in particular, osteoporosis, the disadvantages associated with the use of said fluoride salts can be reduced and/or be avoided.

The invention therefore relates to a pharmaceutical preparation containing a fluoride salt and a steroid with the general formula:



wherein

R_1 = H_2, $H(OR_5)$ or 0;

R_2 = (αR_6) (βOR_7);

R_3 = H or (1-4 C)alkyl in position 6 or 7;

R_4 = (1-4 C)alkyl;

R_5 = H or (1-18 C)acyl;

R_6 = H or (1-4 C)hydrocarbon radical;

R_7 = H or (1-18 C)acyl; and

the broken lines indicate the presence of an additional bond in the 4,5- or 5,10-position.

(1-4 C)Alkyl is understood to mean methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert-butyl. R_3 is preferably methyl and is, in addition, preferably situated in the α-position. R_4 is preferably methyl.

As is already indicated by the affix (1-18 C), (1-18 C) acyl is derived from an organic carboxylic acid containing 1-18 carbon atoms. As examples thereof mention may be made of: formic acid, acetic acid, propionic acid, butyric acid, isobutyric acid, trimethylacetic acid, valeric acid, caproic acid, capric acid, pelargonic acid, undecylenic acid, lauric acid, palmitic acid, oleic acid, phenylacetic acid, phenylpropionic acid, cyclopentylpropionic acid, cyclohexylcarboxylic acid, cyclooctylacetic acid, benzoic acid, fumaric acid, maleic acid, succinic acid, citric acid.

(1-4 C)Hydrocarbon radical is understood to mean one of the groups designated above as (1-4 C)alkyl or an unsaturated variant thereof containing 2-4 carbon atoms, such as vinyl, ethynyl, allyl, propargyl, isopropenyl, butynyl or butadienyl.

R_6 is preferably ethynyl, R_7 then preferably being H.

Salts which are readily soluble in water such as NaF, KF and Na_2PO_3F are preferably used as fluoride salts. The greatest preference is for Na_2PO_3F.

Examples of steroids having the formula I which may be used according to the invention are:
17α-ethyl-17β-hydroxy-Δ^4-oestrene,
17β-hydroxy-Δ^4-oestren-3-one,
7α-methyl-17α-ethynyl-17β-hydroxy-$\Delta^{5(10)}$-oestren-3-one,
7α-methyl-17α-ethynyl-$\Delta^{5(10)}$-oestren-17β-ol,
7α-methyl-17α-ethynyl-17β-hydroxy-Δ^4-oestren-3-one,
7α-methyl-17α-ethyl-17β-hydroxy-$\Delta^{5(10)}$-oestren-3-one,
7α-methyl-17α-ethynyl-$\Delta^{5(10)}$-oestrene-3α,17β-diol,
7α-methyl-17α-ethynyl-$\Delta^{5(10)}$-oestrene-3β,17β-diol,
7α-methyl-17α-allyl-17β-hydroxy-$\Delta^{5(10)}$-oestren-3-one,
7α,17α-dimethyl-17β-hydroxy-Δ^4-oestren-3-one,
7α-methyl-17α-ethynyl-Δ^4-oestrene-3β,17β-diol,
6α-methyl-17β-hydroxy-Δ^4-oestren-3-one,
6α-methyl-17β-hydroxy-Δ^4-oestren-3-one,
6α-methyl-17α-ethynyl-17β-hydroxy-Δ^4-oestren-3-one,
6α-methyl-17α-ethyl-17β-hydroxy-Δ^4-oestren-3-one,
6α-methyl-17α-ethynyl-Δ^4-oestren-17β-ol,
6α-methyl-17α-ethynyl-17β-hydroxy-$\Delta^{5(10)}$-oestren-3-one,
6α-methyl-17α-allyl-17β-hydroxy-$\Delta^{5(10)}$-oestren-3-one, and esters thereof. The greatest preference is for 7α-methyl-17α-ethynyl-17β-hydroxy-$\Delta^{5(10)}$-oestren-3-one.

The pharmaceutical preparations according to the invention can be prepared by known galenical techniques by converting the respective steroid compound and the fluoride salt into a form which is suitable for enteral (for example, oral or rectal, and preferably oral) use. For this purpose, the steroid compound and the fluoride salt are mixed with or dissolved in a pharmaceutically acceptable carrier.

Examples of such preparations are tablets, pills, dragees, pastilles, suppositories, powders, (micro)capsules, emulsions, suspensions and solutions.

The quantity of steroid in the preparation to be administered is 0.05-10.0 mg and usually 0.1-5.0 mg. The quantity of fluoride salt in the preparations to be administered is 1-250 mg and usually 10-100 mg. The daily dosage is usually 1-3 dosage units.

The pharmaceutically acceptable carriers may be composed of one or more of the following ingredients: starch (for example, potato starch, maize starch), sugars (for example, lactose), lubricants (magnesium stearate, stearic acid), binders (for example, amylopectin, polyvinylpyrrolidone), water, alcohol, glycerol and derivatives thereof, vegetable, animal and mineral oils and fats, fatty alcohols, silicones, lanolins, polyalkylene glycols, cellulose derivatives, silica, dispersants, emulsifiers, surface active substances, antioxidants, preservatives, etc.

The preparations according to the invention may suitably be used to prevent and/or treat diseases which occur as a consequence of an excessively low bone substance and in particular, of osteoporosis.

The invention is explained on the basis of the following examples.

Example 1 (tablet)

7α-Methyl-17α-ethynyl-17β-hydroxy-$\Delta^{5(10)}$-oestren-3-one,	2.5 mg
Na_2PO_3F	50.0 mg
Potato starch	25.0 mg
Magnesium stearate	1.25 mg
Ascorbyl palmitate	0.5 mg
Amylopectin	5.0 mg
Lactose to	250.0 mg

Example 2 (tablet)

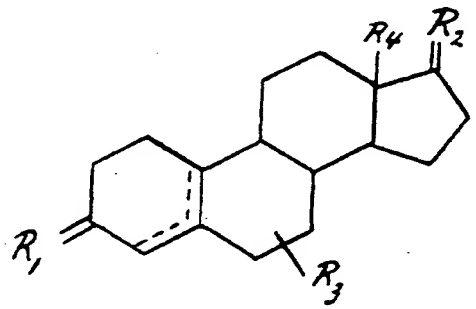
7α-Methyl-17α-ethyl-17β-hydroxy-$\Delta^{5(10)}$-oestren-3-one,	2.0 mg
Na_2PO_3F	30.0 mg
Maize starch	25.0 mg
Stearic acid	2.5 mg
Silica ("Aerosil")	2.5 mg
Polyvinylpyrrolidone	7.5 mg
dl-α-Tocopherol	0.25 mg
Lactose to	250.0 mg

Example 3 (tablet)

7α-Methyl-17α-ethynyl-17β-hydroxy-Δ4-oestren-3-one,	5.0 mg
Na_2PO_3F	50.0 mg
Potato starch	62.5 mg
Magnesium stearate	10.0 mg
dl-α-Tocopherol	0.5 mg
Lactose to	250.0 mg

Claims

1. Pharmaceutical preparation containing a fluoride salt and a steroid with the general formula:



wherein

R_1 = H_2, $H(OR_5)$ or 0;

R_2 = (αR_6) $(\beta 0R_7)$;

R_3 = H or (1-4 C)alkyl in position 6 or 7;

R_4 = (1-4 C)alkyl;

R_5 = H or (1-18 C)acyl;

R_6 = H or (1-4 C)hydrocarbon radical;

R_7 = H or (1-18 C)acyl; and

the broken lines indicate the presence of an additional bond in the 4,5- or 5,10-position.

2. Pharmaceutical preparation according to Claim 1, characterized in that the fluoride salt is water-soluble.

3. Pharmaceutical preparation according to Claim 1-2, characterized in that the fluoride salt is a sodium salt.

4. Pharmaceutical preparation according to Claim 1-3, characterized in that the fluoride salt is Na_2PO_3F.

5. Pharmaceutical preparation according to Claim 1-4, characterized in that the steroid is 7α-methyl-17α-ethynyl-17β-hydroxy-$\Delta^{5(10)}$-oestren-3-one.

6. Pharmaceutical preparation according to Claim 1-5, characterized in that the quantity of steroid is 0.05-10.0 mg.

7. Pharmaceutical preparation according to Claim 1-6, characterized in that the quantity of salt is 1-250 mg.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 89/00326

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 33/16, A 61 K 33/42,//(A 61 K 33/42, 33:16, 31:565)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 3287219 (CHARLES J. NEMANICK) 22 November 1966 --	1-7
A	Rote Liste, 1980, Editio Cantor (Aulendorf, Württ., DE), no. 61051 B, "Calstabil" ----	1-7

* Special categories of cited documents: [10]

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21st July 1989	11 AUG 1989
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

Form PCT/ISA/210 (second sheet) (January 1985)

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/08/89
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US-A- 3287219		None	